Palladium-catalyzed Stereospecific Epoxide-opening Reaction of γ,δ-Epoxy-α,β-unsaturated Esters with Boric Acid Leading to γ,δ-Diol Derivatives with Double Inversion of Configuration

Xiao-Qiang Yu, Atsushi Hirai, and Masaaki Miyashita*
Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo, 060-0810

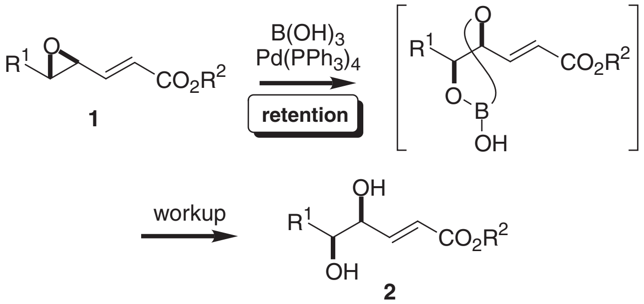
(Received March 18, 2004; CL-040306)

A new palladium-catalyzed epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with boric acid has been developed, which proceeds stereospecifically giving rise to the corresponding γ,δ-diol derivatives with double inversion of the configuration, i.e., with retention of configuration, in excellent yields. The new method provides a useful tool in organic synthesis including natural product synthesis.

The epoxide-opening reaction with nucleophiles is an extremely important transformation in organic synthesis, particularly, in context with the stereoselective synthesis of functionalized chiral compounds such as biologically active natural products.[1] It is well known that the substitution reaction of a *trans*-epoxide with a nucleophile generally gives an *anti*-product via an S_N2 process. When a hydroxide ion is used as a nucleophile, the corresponding *anti*-diol is stereoselectively formed. On the contrary, in order to synthesize the corresponding *syn*-diol from a *trans*-epoxide in a stereoselective manner, ingenuity to perform the epoxide-opening reaction with retention of configuration is required. However, in general, such synthetic transformation is known to be difficult, although a few particular cases have been reported.[2]

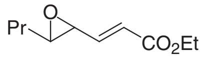
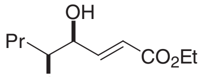
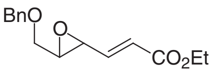
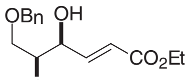
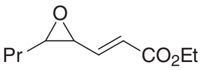
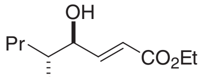
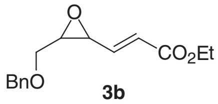
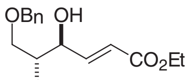
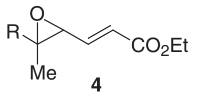
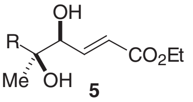
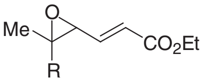
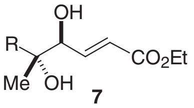
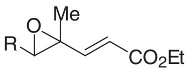
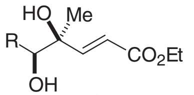
As our program toward the development of the stereospecific substitution reactions of epoxides, we recently reported a new type of palladium-catalyzed stereospecific epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with an alkylboronic acid which proceeds with double inversion of the configuration, that is, retention of configuration, to afford cyclic boronates in good yields.[3] Although these cyclic boronates were convertible into the corresponding γ,δ-diols by treatment with hydrogen peroxide in high yields, this method needed not only the use of expensive butylboronic acid but also two steps for the net conversion of epoxides into diols. In addition, we encountered considerable decrease in yield in the reactions of *cis*-epoxy unsaturated esters in contrast with that in the reactions of *trans*-epoxides. In order to overcome these synthetic limitations, we newly designed a palladium-catalyzed epoxide-opening reaction of γ,δ-epoxy unsaturated esters with boric acid, $B(OH)_3$, for this particular conversion (Scheme 1). In this paper, we report the direct and more efficient method for the conversion of γ,δ-epoxy unsaturated esters to γ,δ-vicinal diols with retention of configuration.

Initially, we examined the reaction of *trans*-4,5-epoxy-2-octenoate (**1a**)[4] with boric acid in the presence of a palladium catalyst ($Pd(PPh_3)_4$) to confirm whether or not the desired reaction indeed takes place. Thus, when boric acid (1.3 equiv.) and a palladium catalyst ($Pd(PPh_3)_4$, 5 mol %) was added to a solution of **1a** in THF and the resulting mixture was stirred at room temper-



Scheme 1. Stereospecific epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with $B(OH)_3$ with retention of configuration.

Table 1. Stereospecific conversion of γ,δ-epoxy-α,β-unsaturated esters to γ,δ-vicinal diols with retention of configuration.

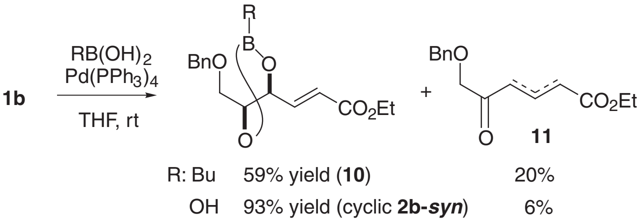
Entry	Substrate	Product	Yield/%[a]	dr[b]
1	 **1a**	 **2a-*syn***	96 (91)	98:2 (99:1)
2	 **1b**	 **2b-*syn***	93 (94)	98:2 (99:1)
3	 **3a**	 **2a-*anti***	89 (71)	98:2 (95:5)
4	 **3b**	 **2b-*anti***	85 (75)	96:4 (95:5)
5[c]	 **4**	 **5**	95 (94)	97:3 (97:3)
6[c]	 **6**	 **7**	86 (76)	97:3 (97:3)
7[d]	 **8**	 **9**	92	99:1

[a] Yields in parentheses are those obtained by the previous procedure.[3] [b] Determined by ^{13}C NMR; Ratios in parentheses are diastereoselectivity by the previous method. [c] $R = (CH_3)_2C{=}CH(CH_2)_2$. [d] $R = Ph(CH_2)_2$.

ature, the epoxide-opening reaction with double inversion of the configuration did occur giving rise to the desired product **2a-*syn***. Notably, the reaction was very fast and completed in 10 min at room temperature, and **2a-*syn*** was obtained in 96% isolated yield by passing the reaction mixture through a silica gel column followed by purification.

The excellent preliminary results led us to examine the scope of the new synthetic reaction with various substrates. The results are summarized in Table 1.[5] The reactions of disubstituted *trans*-γ,δ-epoxy-α,β-unsaturated esters **1a** and **1b** proceeded smoothly to give **2a-*syn*** and **2b-*syn*** in excellent yield, respectively (Entries 1 and 2). The stereoselectivity of each product was found to be 98:2 from its ^{13}C NMR spectrum.[6] Similarly, the corresponding disubstituted *cis*-congeners also reacted smoothly to produce the **2a-*anti*** and **2b-*anti*** diols stereospecifically in 89 and 85% yields, respectively (Entries 3 and 4). Noteworthy is that the yields of *anti*-diols derived from *cis*-epoxides were much higher than those obtained by the previous method (Entries 3 and 4). In turn, we examined trisubstituted epoxy unsaturated esters **4**, **6**, and **8** prepared from geraniol, nerol, and 2-methyl-5-phenyl-2-pentenoate, respectively (Entries **5–7**). These substrates also smoothly and cleanly reacted to afford the corresponding vicinal diols in a highly-stereoselective manner which contain contiguous secondary and tertiary alcohols. It should be pointed out that the yield of **7** was also improved substantially by the present method.

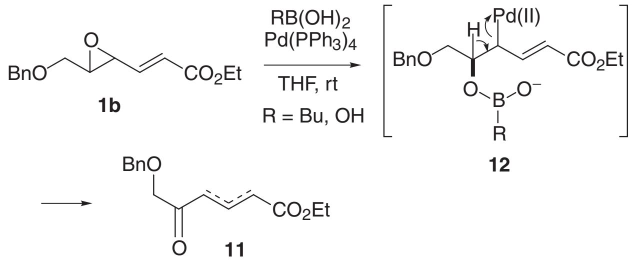
To demonstrate the synthetic potential of the present method, the reactions of **1b** with butylboronic acid (BuB(OH)$_2$) and with B(OH)$_3$ were compared (Scheme 2). Thus, the reaction of **1b** with B(OH)$_3$ produced **2b-*syn*** in excellent yield as already mentioned, whereas the reaction with BuB(OH)$_2$ afforded the desired cyclic boronate **10** only in moderate yield and unexpected ketones **11** were formed considerably in the latter reaction. These results obviously demonstrate that the reaction with B(OH)$_3$ is much superior to the previous method using BuB(OH)$_2$.



Scheme 2. The reactions of **1b** with BuB(OH)$_2$ and with B(OH)$_3$.

Remarkable discrepancy in these reactions may be rationalized as follows. As shown in Scheme 3, these reactions proceed via π-allyl palladium species **12** wherein a borate anion (R = OH) acts as an efficient nucleophile to give a cyclic borate (cyclic **2b-*syn***) smoothly, while a boronate anion (R = Bu) probably does not act as an effective nucleophile due to its steric and/or electronic factors and consequently undergoes a β-elimination reaction concomitantly resulting in the formation of ketones **11**. The stability of the cyclic **2b-*syn*** in the reaction is also conceivable.

In summary, we have developed a new palladium-catalyzed epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with boric acid which gives γ,δ-diol derivatives with double inversion of the configuration in excellent yields. The new method is applicable to various disubstituted *cis*- and *trans*-γ,δ-epoxy unsaturated esters and directly affords vicinal γ,δ-diols in a highly-stereoselective manner. The method is also applicable to trisubstituted epoxides, wherein the products including vicinal secondary and tertiary alcohols are obtainable in high yields. Since it is known that asymmetric dihydroxylation with chiral osmium reagents can not be applied to disubstituted *cis*-olefins,[7] the present method provides an extremely useful tool in organic synthesis including natural product synthesis.



Scheme 3. Formation of ketones **11** in the reactions of **1b** with Bu(OH)$_2$ and with B(OH)$_3$.

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan (a Grant-in-Aid for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" (No. 13029003)). We are grateful to High-Resolution NMR Laboratory, Hokkaido University, for measuring ^{13}C NMR spectra.

References and Notes

1 B. M. Kim, et al., in "Comprehensive Organic Synthesis, Additions to C–X π-Bonds, Part 2," ed. by C. H. Heathcock, Pergamon Press, Oxford (1991), Vol. 2, Chap. 1.7.

2 H. Hayakawa, N. Okada, and M. Miyashita, *Tetrahedron Lett.*, **40**, 3191 (1999).

3 A. Hirai, T. Tonooka, K. Wakatsuki, K. Tanino, and M. Miyashita, *Chirality*, **15**, 108 (2003); A. Hirai, X.-Q. Yu, T. Tonooka, and M. Miyashita, *Chem. Commun.*, **2003**, 2482.

4 *trans*- and *cis*-γ,δ-Epoxy unsaturated esters were prepared from the allyl alcohols by the three step reaction sequence: 1) epoxidation with *m*CPBA; 2) Swern oxidation; 3) Horner–Wadsworth–Emmons reaction with triethyl phosphonoacetate.

5 **Typical procedure for the epoxide-opening reaction of γ,δ-epoxy-α,β-unsaturated esters with B(OH)$_3$:** To a solution of **1a** (53 mg, 0.2 mmol) in THF (1 mL) was added B(OH)$_3$ (27 mg, 0.26 mmol) and Pd(PPh$_3$)$_4$ (12 mg, 0.01 mmol) and the mixture was stirred at room temperature for 10 min. The reaction mixture was passed through a silica gel column by the aid of EtOAc and the eluate was concentrated in vacuo to leave the crude diol. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 7:3) to give the **2a-*syn*** diol (53 mg, 94% yield).

6 Stereochemistry of the products was unambiguously determined by NOE measurements of the acetonides derived from **2b-*syn*** and **2b-*anti***, respectively.

7 L. Wang and K. B. Sharpless, *J. Am. Chem. Soc.*, **114**, 7568 (1992); Asymmetric dihydroxylation of dienes, see: D. Xu, G. A. Crispino, and K. B. Sharpless, *J. Am. Chem. Soc.*, **114**, 7570 (1992).